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Proposed Registration Decision PRD2015-31

Male Sea Lamprey Mating Pheromone

(3-ketopetromyzonol-24-sulfate, ammonium salt)

(publié aussi en français)

18 December 2015

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2015-31E (print version)
H113-9/2015-31E-PDF (PDF version)

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Table of Contents

Overview 1
Proposed Registration Decision for Male Sea Lamprey Mating Pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) 1
What Does Health Canada Consider When Making a Registration Decision? 1
What Is Male Sea Lamprey Mating Pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt)? 2
Health Considerations 2
Environmental Considerations 4
Value Considerations 4
Measures to Minimize Risk 4
Next Steps 5
Other Information 5
Science Evaluation 7
1.0 The Active Ingredient, Its Properties and Uses 7
1.1 Identity of the Active Ingredient 7
1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product 7
1.3 Directions for Use 9
1.4 Mode of Action 9
2.0 Methods of Analysis 9
2.1 Methods for Analysis of the Active Ingredient 9
2.2 Method for Formulation Analysis 9
3.0 Impact on Human and Animal Health 10
3.1 Toxicology Summary 10
3.2 Occupational and Bystander Exposure and Risk Assessment 11
3.2.1 Dermal Absorption 11
3.2.2 Use Description 11
3.2.3 Mixer, Loader, and Applicator Exposure and Risk 11
3.2.4 Postapplication Worker Exposure and Risk 11
3.2.5 Residential and Bystander Exposure and Risk 11
3.3 Food Residue Exposure Assessment 12
3.3.1 Food and Drinking Water 12
3.3.2 Maximum Residue Limits (MRLs) 12
4.0 Impact on the Environment 12
4.1 Fate and Behaviour in the Environment 12
4.2 Environmental Risk Characterization 13
4.2.1 Risks to Terrestrial Organisms 13
4.2.2 Risks to Aquatic Organisms 13

5.0 Value 14
5.1 Consideration of Benefits 14
5.2 Effectiveness Against Pests 14
5.3 Supported Uses 14
6.0 Pest Control Product Policy Considerations 14
6.1 Toxic Substances Management Policy Considerations 14
6.2 Formulants and Contaminants of Health or Environmental Concern 15
7.0 Summary 16
7.1 Human Health and Safety 16
7.2 Environmental Risk 16
7.3 Value 17
8.0 Proposed Regulatory Decision 17
List of Abbreviations 19
Appendix I Tables and Figures 21
Table 1 Toxicity Profile of Male Sea Lamprey Mating Pheromone Containing 3-Ketopetromyzonol-24-Sulfate, Ammonium Salt 21
Table 2 Toxicity Profile of Technical Ammonium Salt of 3-Ketopetromyzonol-24-sulfate 22
Table 3 Fate and Behaviour in the Environment 23
Table 4 Toxic Substances Management Policy Considerations 23
References 25

Overview

Proposed Registration Decision for Male Sea Lamprey Mating Pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt)

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Male Sea Lamprey Mating Pheromone Technical and Male Sea Lamprey Mating Pheromone, containing the technical grade active ingredient male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt), for use in streams and tributaries of the Great Lakes and Lake Champlain as an attractant for reproductively mature female sea lampreys. The purpose of Male Sea Lamprey Mating Pheromone is to lure the female sea lampreys into traps for removal during the spawning season.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt).

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt), the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt), which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Male Sea Lamprey Mating Pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt)?

Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is a synthetic version of a sex pheromone produced by adult male sea lampreys to attract adult female sea lampreys for mating. Male Sea Lamprey Mating Pheromone is used to attract female sea lampreys into traps for removal, to prevent mating and ultimately reduce sea lamprey populations.

Health Considerations

Can Approved Uses of Male Sea Lamprey Mating Pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) Affect Human Health?

Male Sea Lamprey Mating Pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is unlikely to affect human health when it is used according to label directions.

Potential exposure to male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) may occur when handling and applying the end-use product, Male Sea Lamprey Mating Pheromone. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

The acute toxicity of the end-use product, Male Sea Lamprey Mating Pheromone, was low via the oral, dermal, and inhalation routes of exposure. Male Sea Lamprey Mating Pheromone is not irritating to the skin but is non- to slightly irritating to the eyes. Male Sea Lamprey Mating Pheromone is not a dermal sensitizer.

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[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The active ingredient, male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt), was considered to be of high acute toxicity via the oral route of exposure; consequently, the hazard signal words "DANGER POISON" are required on the Male Sea Lamprey Mating Pheromone Technical label. Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) may be irritating to the skin and eyes; consequently, the hazard signal words "MAY BE AN EYE AND SKIN IRRITANT" are required on the Male Sea Lamprey Mating Pheromone Technical label. Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is not a dermal sensitizer.

Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is not expected to cause effects in developing young or to cause damage to genetic material when used according to the label instructions.

The risk assessment protects against the effects of male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) by ensuring that the level of human exposure is well below the lowest dose at which effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is not proposed for food or feed use, and its application to water bodies populated by sea lampreys is not expected to exceed natural background levels. Dietary risk from food and drinking water is therefore expected to be negligible and not of concern.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for residential and other non-occupational exposure is not of concern.

Residential exposure to individuals coming in contact with Male Sea Lamprey Mating Pheromone during application is not expected to result in unacceptable risk when Male Sea Lamprey Mating Pheromone is used according to label directions.

Occupational Risks From Handling Male Sea Lamprey Mating Pheromone

Occupational risks are not of concern when Male Sea Lamprey Mating Pheromone is used according to the label directions, which include protective measures.

An assessment conducted for individuals handling and applying Male Sea Lamprey Mating Pheromone indicated that the risk is not of concern when the product is used according to label directions.

Environmental Considerations

What Happens when Male Sea Lamprey Mating Pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is Introduced Into the Environment?

Male Sea Lamprey Mating Pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is not expected to pose an unacceptable risk to the environment when used according to the product label instructions.

Male Sea Lamprey Mating Pheromone is applied directly to stream water at a concentration that is intended to augment (not exceed) natural background levels of the pheromone produced by male sea lamprey to attract females during time of spawning (spring to early summer). The product is applied only when the natural pheromone is being produced by the male lamprey, and will break down rapidly once in the environment. When applied at levels similar to those occurring naturally, the pheromone is not considered toxic to non-target aquatic organisms.

Value Considerations

What Is the Value of Male Sea Lamprey Mating Pheromone?

Male Sea Lamprey Mating Pheromone provides an additional tool to aid in the management of invasive sea lampreys in the Great Lakes and Lake Champlain.

Male Sea Lamprey Mating Pheromone may be used to attract adult females into traps. Limiting reproduction of sea lampreys by trapping adult females could reduce or eliminate the need to treat the subsequent generation of young lampreys with pesticides. By lowering the sea lamprey population in the Great Lakes and Lake Champlain, the mortality sea lamprey cause to several fish species would be reduced, aiding in the restoration of those native fish populations.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Male Sea Lamprey Mating Pheromone Technical and Male Sea Lamprey Mating Pheromone to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Male Sea Lamprey Mating Pheromone Technical labels must include the statement, "DANGER POISON" and "MAY BE AN EYE AND SKIN IRRITANT" on the principal display panel and "Fatal or Poisonous if swallowed", "May irritate skin and eyes" and "Avoid contact with the skin and eyes" on the secondary display panel.

Environment

Risk to non-target animals and plants will be minimal through the proposed use of this pheromone product. Therefore, key risk-reduction measures for the protection of the environment are not required.

Next Steps

Before making a final registration decision on male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt), the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

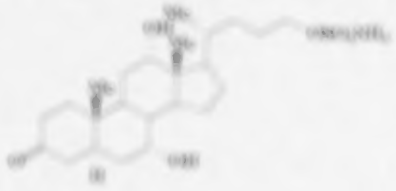
When the PMRA makes its registration decision, it will publish a Registration Decision on male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Male Sea Lamprey Mating Pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt)

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	3-ketopetromyzonol-24-sulfate, present as ammonium salt
Function	Mating pheromone
Chemical name	
1. **International Union of Pure and Applied Chemistry (IUPAC)**	ammonium 3-[(8*S*,7*R*,10*S*,12*S*,13*R*)-7,12-dihydroxy-10,13-dimethyl-3-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]propyl sulfate
2. **Chemical Abstracts Service (CAS)**	Cholan-3-one, 7,12-dihydroxy-24-(sulfooxy)-, (5 alpha ,7 alpha ,12 alpha)-
CAS number	435327-06-3
Molecular formula	$C_{24}H_{41}NO_8S$
Molecular weight	609.67
Structural formula	
Purity of the active ingredient	98.5%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Male Sea Lamprey Mating Pheromone Technical

Property	Result
Colour and physical state	White solid
Odour	No odour
Melting range	185-187°C
Boiling point or range	N/A

Property	Result
Specific gravity	1.3050
Vapour pressure at 20°C	Not required for this product
Ultraviolet (UV)-visible spectrum	Conditions: λ_{max} (nm); ε (L/mole·cm) Acidic: 277.20; 20.42 290.00; 19.66 295.00; 16.39 300.00; 6.06 310.00; 1.78 Alkaline: 212.16; 210.57 278.00; 25.98 290.00; 19.98 295.00; 17.03 300.00; 7.17 310.00; 3.09
Solubility in distilled water at 19.8°C and in buffered water at 20°C	pH: Solubility (mg/mL): Unbuffered water: 46.81 10: 20.46 8: 12.89
Solubility in organic solvents at 20°C	Not required for this product
n-Octanol-water partition coefficient (K_{ow})	N/A
Dissociation constant (pK_a)	Log pK_a = 2.55
Stability (temperature, metal)	Stable when stored for two weeks on its own and in the presence of aluminium, iron, zinc, aluminium acetate, iron acetate, zinc acetate and water at 54°C

End-Use Product — Multi-Use Lacquer Thinning Thermoset

Property	Result
Colour	Colourless
Odour	Slightly alcoholic
Physical state	Liquid
Formulation type	Solution
Guarantee	1.08%
Container material and description	10 mL of the product is packaged in 15 mL polypropylene vials
Density	0.93 g/cm^3
pH of 1% dispersion in water	6.1

Property	Result
Oxidizing or reducing action	N/A
Storage stability	Stable for at least two years when stored in an ultra-cold freezer and for at least four days when stored at room temperature
Corrosion characteristics	Not corrosive to the storage container
Explosibility	When in use could form a flammable/explosive vapour-air mixture and could be a moderate explosive hazard

1.5 Directions for Use

Male Sea Lamprey Mating Pheromone is applied directly into the water in conjunction with traps in streams of the Great Lakes and Lake Champlain watershed where sea lampreys are known to spawn. The objective is to lure female sea lampreys into the traps for removal and thus reduce sea lamprey reproduction. The application rate is calculated based on measured stream flow at the site of application and is the amount of product required to achieve a concentration between 1×10^{-12} and 1×10^{-11} M (0.0972 – 0.72 ppt) in the stream. Application is made continuously from sunset to sunrise (activity of sea lampreys migrating upstream to spawn is nocturnal) throughout the season of sea lamprey migration and spawning.

1.6 Mode of Action

The active, male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt), is a synthetic version of the pheromone found to be released by reproductively mature male sea lampreys and shown to be attractive to reproductively mature female sea lampreys; therefore, it is considered to be a sea lamprey sex pheromone. It acts by stimulating adult female sea lampreys to swim upstream until they reach the source of the pheromone.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) was conducted by the PMRA. The database for male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is considered adequate (Tables 1 and 2, Appendix I), consisting of in vitro toxicity studies (acute oral, dermal, and inhalation toxicity, skin and eye irritation, and dermal sensitization), publicly available information on the structurally similar carp bile salt, 5α-cyprinol sulfate, and rationales to waive short-term toxicity, prenatal developmental toxicity, and genotoxicity. The scientific quality of the data is such that the database is considered adequate to assess the toxic effects that may result from exposure to male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt).

In lieu of in vivo studies and based on available information on carp bile salts, male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is considered highly acutely toxic by the oral route. Insufficient information is available to determine the hazard associated with acute exposure by the dermal or inhalation routes to male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt). Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is expected to irritate the eyes and possibly the skin, but the severity could not be determined using the available in vitro information. Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is not expected to be a dermal sensitizer. Based on the composition of Male Sea Lamprey Mating Pheromone (1.1 % w/w male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt), low acute oral, dermal, and inhalation toxicity is anticipated. Male Sea Lamprey Mating Pheromone is expected to be non- to slightly irritating to the eyes, but is not expected to be a dermal irritant or a dermal sensitizer.

Waivers were granted for the short-term toxicity, prenatal developmental toxicity, and genotoxicity based on the minimal exposure expected when used according to label directions, which includes adherence to label precautions.

The formulants in Male Sea Lamprey Mating Pheromone are supported for the proposed use in non-food aquatic sites.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the mandatory reporting of incidents can be found on the Health Canada website. Incidents from Canada and the United States were searched and reviewed for 3-ketopetromyzonol-24-sulfate, ammonium salt. As of 24 September 2015, there were no incident reports submitted to the PMRA, USEPA, or California EPA.

3.2 Occupational and Bystander Exposure and Risk Assessment

3.2.1 Dermal Absorption

Dermal absorption of Male Sea Lamprey Mating Pheromone is not expected to be of concern due to the molecular weight of the active ingredient (MW = 489.67), the water solubility (46.41 mg/mL in unbuffered double distilled water), and the anticipated low toxicity via the dermal route.

3.2.2 Use Description

Male Sea Lamprey Mating Pheromone is proposed for aquatic use in non-food sites. The method of application is by direct dripping of diluted end-use product into the sea lamprey trap using a battery operated peristaltic pump (an in-stream concentration of 1×10^{-11} M to 1×10^{-13} M). Male Sea Lamprey Mating Pheromone is applied over 30 to 90 days during the sea lamprey migratory and spawning season (April through July). The applications occur every night (8 to 12 hours per night depending on the length of the day). The maximum amount of the active ingredient handled per day varies depending on the stream's rate of discharge (in other words, a discharge rate of 1 m^3/s would result in the handling of 0.00015 g a.i/day. to 0.015 g a.i/day; a discharge rate of 10 m^3/s would result in the handling of 0.0015 g a.i./day to 0.15 g a.i./day).

3.2.3 Mixer, Loader, and Applicator Exposure and Risk

Exposure to workers mixing, loading, and applying Male Sea Lamprey Mating Pheromone is expected to be short-term in duration and to occur primarily by the dermal route.

The risk due to exposure from mixing, loading, applying, clean-up, and maintenance of machinery for workers is considered to be acceptable when used according to the label, which includes adhering to the label precautions.

3.2.4 Postapplication Worker Exposure and Risk

There is a potential for exposure to workers re-entering areas treated with Male Sea Lamprey Mating Pheromone. Given the nature of the postapplication activities typically performed (for example, scouting treated areas and lamprey trap maintenance), dermal contact with treated bodies of water is possible. While the degree of exposure will be related to the time of re-entry and the duration of the activities, the potential risk due to exposure resulting from postapplication work is not a concern, regardless of the type and duration of the activity. As the concentration of the pheromone is not expected to exceed background concentrations in waters where sea lamprey are present, a restricted-entry interval is not required.

3.2.5 Residential and Bystander Exposure and Risk

Bystander exposure is possible during postapplication activities, such as swimming, but the concentrations of the exogenous pheromone applied to the body of water will not exceed natural background concentrations. The potential risk due to exposure resulting from postapplication aquatic activities is not a concern, regardless of the type and duration of the activity.

3.3 Food Residue Exposure Assessment

3.3.1 Food and Drinking Water

Male Sea Lamprey Mating Pheromone is not proposed for food or feed use, and its application to water bodies populated by sea lampreys is not expected to exceed natural background levels. Dietary risk from food and drinking water is therefore expected to be negligible and not of concern.

3.3.2 Maximum Residue Limits (MRLs)

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine that the consumption of the maximum amount of residues that are expected to remain on food products when a pesticide is used according to label directions will not be a concern to human health. This maximum amount of residues expected is then legally specified as an MRL under the *Pest Control Products Act* for the purposes of adulteration provision of the *Food and Drugs Act*. Health Canada specifies science-based MRLs to ensure the food Canadians eat is safe.

The dietary risks from food and drinking water are expected to be negligible given that Male Sea Lamprey Mating Pheromone is not proposed for food or feed use, and its application to water bodies populated by sea lampreys is not expected to exceed natural background levels. Consequently, the specification of an MRL for male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) under the *Pest Control Products Act* is not being recommended.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate) is naturally present in tributaries only during the spawning season, generally from April to early July. The addition of the proposed product to tributaries is intended to augment natural levels of the pheromone found in water during the lamprey spawning period. This will elicit a directional response from the females with the intention of luring them into traps. Application of the product is not intended to exceed the natural levels of the pheromone found in the environment.

Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is expected to break down rapidly in the aquatic environment; the 50% dissipation time (time required for 50% of the amount of chemical present in water to be broken down – or DT_{50}) is approximately 1 to 4 days depending on the experimental conditions. By the end of the mating season (late June to July), when application of the product is stopped, coinciding with no further natural production by the male, ambient levels of the pheromone are expected to decrease rapidly. Studies have determined that male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is no longer detected in various sea lamprey infested streams by August after a given spawning season.

Data on the environmental fate and behaviour of male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) are summarized in Appendix I, Table 3.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level). If the generation of quantitative data is not practical for a particular active ingredient/product, a qualitative assessment may be more appropriate.

The environmental risk assessment for male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) was qualitative as the application of the end-use product, Male Sea Lamprey Mating Pheromone, to rivers and streams, is not expected to result in an elevated environmental exposure beyond what occurs naturally at the time of spawning. The estimated environmental exposure concentration will be between 1×10^{-11} to 1×10^{-13} M (4.72 to 0.0472 ng/L), when applied according to label directions. Label instructions also require that water flow is taken into account at each application time. This is similar to, or lower than, natural levels of the pheromone at time of spawning (documented as 0.15 to 120.9 ng/L), depending on the location and measurement time.

4.2.1 Risks to Terrestrial Organisms

Because the product is applied to water, exposure to non-target terrestrial organisms is not expected. Therefore, a risk assessment for terrestrial organisms was not considered further in the review of this product.

4.2.2 Risks to Aquatic Organisms

The product is applied directly to water, so exposure to non-target aquatic organisms will occur. However, as the product is being applied at a concentration that only augments existing natural levels, exposure to non-target aquatic organisms is not expected to be greater than that which occurs naturally during time of spawning. No adverse effects from the naturally occurring compound, or from the product after several years of *in situ* experimental use, have been observed in aquatic organisms. Therefore, risk towards non-target aquatic organisms is not considered to be a concern and was not assessed further.

5.0 Value

5.1 Consideration of Benefits

Male Sea Lamprey Mating Pheromone is a valuable additional management tool for sea lamprey, an invasive parasite that causes significant mortality to native fish such as lake trout and whitefish. The only other available control options are barriers and traps to prevent spawning adults from gaining access to streams and chemical lampricides to kill developing larvae. Male Sea Lamprey Mating Pheromone may be used to maximize capture of adult sea lampreys in existing barrier-integrated trapping systems as well as to lure adult females away from spawning areas and into free-standing traps. The reduction in spawning achieved by removing adult female sea lampreys from the population should reduce and could ultimately eliminate the need to treat subsequent larval lamprey populations with chemical lampricides. Reduction in the use of chemical lampricides would reduce selection pressure for the development of resistance to those products. Only two active ingredients, 3-trifluoromethyl-4-nitrophenol and niclosamide, are registered for use as lampricides in Canada. Overall reductions of sea lamprey populations in the Great Lakes and Lake Champlain reduce the mortality they cause to desirable fish species and thus aid the restoration of those native fish populations.

5.2 Effectiveness Against Pests

In an experimental trial conducted with free-standing traps, significant numbers of adult female sea lampreys were consistently captured in a trap baited with Male Sea Lamprey Mating Pheromone while none were captured in an unbaited control trap in the same stream. In an operational trial conducted over three years using paired barrier-integrated traps in eight different streams, catches of adult sea lampreys in traps baited with Male Sea Lamprey Mating Pheromone were significantly greater than those in unbaited traps. These results demonstrate the ability of Male Sea Lamprey Mating Pheromone to lure adult female sea lampreys into free-standing traps and to increase trapping efficiency of existing barrier-integrated traps.

5.3 Supported Uses

Male Sea Lamprey Mating Pheromone is supported to aid in capturing sea lampreys in traps by application directly into the water in the traps at application rates required to achieve a concentration between 1×10^{-13} and 1×10^{-11} M (0.0472 – 4.72 ppt) in the stream.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) was assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Table 4 for comparison with Track 1 criteria.

- Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) does not contain any impurities and is not expected to form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including DIR99-03[8] and DIR2006-02,[9] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

Male Sea Lamprey Mating Pheromone Technical does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The end-use product, Male Sea Lamprey Mating Pheromone does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

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5 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic SubstancesManagement Policy*.

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern*.

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the *New Pest Control Products Act*.

8 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic SubstancesManagement Policy*.

9 DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is adequate to define the toxic effects that may result from exposure to male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt). The active ingredient, male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt), is anticipated to be of high acute toxicity by the oral route. Exposure to male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is expected to result in eye and, possibly, skin irritation but not dermal sensitization. The end-use product, Male Sea Lamprey Mating Pheromone, is expected to be of low acute toxicity, regardless of the route of exposure, non- to slightly irritating to the eye, but not a dermal irritant or dermal sensitizer. No other toxicologically significant effects are anticipated.

Loaders, mixers, applicators, and workers are not expected to be exposed to levels of male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) that will result in an unacceptable risk due to exposure when Male Sea Lamprey Mating Pheromone is used according to label directions.

Inadvertent bystander exposure during postapplication activities, such as swimming, are not expected to result in an unacceptable risk due to exposure since the concentrations of the exogenous pheromone applied to the body of water will not exceed natural background concentrations.

The dietary risks from food and drinking water are expected to be negligible given that Male Sea Lamprey Mating Pheromone is not proposed for food or feed use, and its application to water bodies populated by sea lampreys is not expected to exceed natural background levels. Consequently, the specification of an MRL under the *Pest Control Products Act* is not being recommended.

7.2 Environmental Risk

Male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt) is not expected to pose an unacceptable risk to the environment when added to water to augment natural levels of the pheromone at time of lamprey spawning.

7.3 Value

Male Sea Lamprey Mating Pheromone provides an additional tool to manage invasive sea lampreys in the Great Lakes and Lake Champlain. Male Sea Lamprey Mating Pheromone increases catches of adult sea lampreys in existing barrier-integrated trapping systems and can lure adult females into free-standing traps. Limiting spawning by trapping adult female sea lampreys could reduce or eliminate the need to treat subsequent larval lamprey populations with chemical lampricides. Lowering sea lamprey populations in the Great Lakes and Lake Champlain should reduce the mortality they cause to other fish species and thus aid the restoration of those native fish populations.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Male Sea Lamprey Mating Pheromone Technical and Male Sea Lamprey Mating Pheromone, containing the technical grade active ingredient male sea lamprey mating pheromone (3-ketopetromyzonol-24-sulfate, ammonium salt), for use in streams and tributaries of the Great Lakes and Lake Champlain as an attractant for reproductively mature female sea lampreys. The purpose of Male Sea Lamprey Mating Pheromone is to lure the female sea lampreys into traps for removal during the spawning season.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
a.i.	active ingredient
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetre
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
EEC	estimated environmental exposure concentration
EP	end-use product
g	gram
hr	hour
hrs	hours
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOD	level of detection
LOQ	limit of quantitation
M	Molar
mg	milligram
mL	millilitre
MAS	maximum average score
MIS	maximum irritation score
MRL	maximum residue limit
N/A	not applicable
nm	nanometre
pH	measure of the acidity or basicity of an aqueous solution
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
ppt	parts per trillion
RQ	risk quotient
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Toxicity Profile of Male Sea Lamprey Mating Pheromone Containing 3-Ketopetromyzonol-24-Sulfate, Ammonium Salt

(Effects are known or assumed to occur in both sexes unless otherwise noted, in such cases, sex-specific effects are separated by semi-colons)

Study Type/ Animal PMRA #	Study Results
Acute oral toxicity PMRA # 2224628	The waiver request submitted does not address the acute effects from oral exposure to undiluted end-use product and is therefore unacceptable. However, based on the composition of the end-use product and the publicly available information, the acute oral toxicity is expected to be low.
Acute dermal toxicity PMRA # 2224628	The waiver request submitted does not address the acute effects from dermal exposure to undiluted end-use product and is therefore unacceptable. However, based on the composition of the end-use product and the publicly available information, the acute dermal toxicity is expected to be low.
Acute inhalation toxicity PMRA # 2224628	The waiver request submitted does not address the acute effects from inhalation of undiluted end-use product and is therefore unacceptable. However, based on the composition of the end-use product and the publicly available information, the acute inhalation toxicity is expected to be low.
Dermal irritation PMRA # 2224628	The waiver request submitted does not address the skin irritation from dermal exposure to undiluted end-use product and is therefore unacceptable. However, based on the composition of the end-use product and the publicly available information, Male Sea Lamprey Mating Pheromone is not expected to be a dermal irritant.
Eye irritation PMRA # 2224628	The waiver request submitted does not address the eye irritation from direct ocular exposure to the end-use product and is therefore unacceptable. However, based on the composition of the end-use product and the publicly available information, Male Sea Lamprey Mating Pheromone is expected to be non- to slightly irritating to the eyes.
Dermal sensitization PMRA # 2224628	Based on the composition of the end-use product, the publicly available information, and the information provided by the applicant, Male Sea Lamprey Mating Pheromone is not expected to be a dermal sensitizer.

Table 2 Toxicity Profile of Technical Grade Salt of 3-Ketopetromyzonol-24-sulfate

(Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type/ Technical PMRA #	Study Results
Acute oral toxicity PMRA # 2301054	The toxicological properties of a structurally similar component, *CASP Toxin* (7α-cygromol sulfate), and the general lack of toxicological information pertaining to the male sea lamprey mating pheromone suggests that a conservative approach be taken. As such, the acute oral toxicity is considered to be high for 3-Ketopetromyzonol-24-Sulfate, Ammonium Salt
Acute dermal toxicity PMRA # 2224178	Based on the *in vitro* dermal absorption study submitted, the acute dermal toxicity of 3-Ketopetromyzonol-24-Sulfate, Ammonium Salt *could* not be determined
Acute inhalation toxicity PMRA #2224179	Based on the non-guideline *in vitro* study, submitted by the applicant, the acute inhalation toxicity of 3-Ketopetromyzonol-24-Sulfate, Ammonium Salt *could* not be determined
Dermal irritation PMRA # 2224176	Based on the *in vitro* study, submitted by the applicant, the primary skin irritation of 3-Ketopetromyzonol-24-Sulfate, Ammonium Salt *could* not be determined. Publicly available information suggests that bile salts, bile acids, and bile alcohols may act as dermal irritants, but the severity varies depending on the class, structure, water solubility, *etc*
Eye irritation PMRA # 2224177	Based on the non-guideline *in vitro* study, submitted by the applicant, the primary eye irritation of 3-Ketopetromyzonol-24-Sulfate, Ammonium Salt *could* not be determined. However, publicly available information suggests that bile salts, bile acids, and bile alcohols may act as ocular irritants, the severity of which varies.
Dermal sensitization PMRA # 2224181	Based on the *in vitro* study, submitted by the applicant, the dermal sensitization of 3-Ketopetromyzonol-24-Sulfate, Ammonium Salt *could* not be determined. However, based on similarly structured bile salt, acids, and alcohols it is unlikely that 3-Ketopetromyzonol-24-Sulfate, Ammonium Salt is a dermal sensitizer
Short-term Oral Toxicity PMRA # 2224620	The waiver request for short-term oral toxicity was accepted on the basis that minimal exposure is expected if the label directions and precautions are followed
Prenatal Developmental Toxicity PMRA # 2224620	The waiver request for prenatal developmental toxicity was accepted on the basis that minimal exposure is expected if the label directions and precautions are followed

Study Type/ Guideline (PMRA #)	Study Results
Genotoxicity: bacterial reverse mutation assay PMRA #: [redacted]	The waiver request for the bacterial reverse mutation assay data requirement was accepted on the basis that minimal exposure is expected if the label directions and precautions are followed.
Genotoxicity: *in vitro* mammalian cell assay PMRA #: [redacted]	The waiver request for the *in vitro* mammalian cell assay data requirement was accepted on the basis that minimal exposure is expected if the label directions and precautions are followed.

Table 3 Fate and Behaviour in the Environment

Study	Data reference	Value	Remarks	Reference (PMRA #)
Not rated - assumed to be aerobic biotransformation in water	835.5: Hydrolysis, pH 5, 7, and 9 (abiotic, sterile, aqueous, pH dictated by buffer used)	$t_{1/2}$ > 30 d	conducted in a simulated sterile environment	[redacted]
Not rated - assumed to be aerobic biotransformation in water	manually accounting for hydrolysis, aqueous, aerobic	DT_{50} at 4°C = 6.2 days	conducted with unprocessed stream samples stored at 4°C	[redacted]

Table 4 Toxic Substances Management Policy Considerations

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Hydrogeotrioxonedi-2e-sulfate, ammonium salt ingredient
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*	Yes		no
Predominantly anthropogenic	Yes		yes
Persistence	And	HalfLife ≥ 182 days	N/A

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		3-ketopetromyzonol-24-sulfate, ammonium salt endpoints
	Water	Half-life ≥ 182 days	3-ketopetromyzonol-24-sulfate, ammonium salt DT_{50}: 4.2-26.1 days
	Sediment	Half-life ≥ 365 days	N/A
	Air	Half-life ≥ 2 days or evidence of long range transport	N/A
Bioaccumulation[5]	Log K_{OW} ≥ 5		N/A
	BCF ≥ 5000		N/A
	BAF ≥ 5000		N/A
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria

[4] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (i.e., all other TSMP criteria are met).
[5] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[6] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) then the criterion for persistence is considered to be met.
[7] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2224570	2009, Purity analysis on synthesized 3kPZS, DACO: 2.13.1, 2.13.2, 2.13.3, CBI
2224571	2011, Physical and Chemical Properties of 3-ketopetromyzonol-24-sulfate, ammonium salt, DACO: 2.14.1, 2.14.11, 2.14.14, 2.14.2, 2.14.3, 2.14.5, 2.14.9, 3.5.1, 3.5.10, 3.5.14, 3.5.2, 3.5.3, 3.5.7, CBI
2224572	2010, Male Sea Lamprey Mating Pheromone Evaluation of Selected Physical Chemical Properties, DACO: 2.14.10, 2.14.12, 2.14.13, 2.14.4, 2.14.6, 2.14.7, 2.14.8, 3.5.10, 3.5.6, CBI
2301047	2012, Description of Starting Materials and Detailed Production Process from [CBI removed], DACO: 2.11.2, 2.11.3 CBI
2301050	2013, Clarification on Methodology/Validation and Batch Data, DACO: 2.13.1, 2.13.3 CBI
2301051	2013, Clarification on Impurities, DACO: 2.13.2 CBI
2302287	2009, Appendix 4 - Manufacturing Process - additional information from [CBI removed], DACO: 2.11.1, 2.11.3, 2.11.4, CBI
2302288	2009, Appendix 3 - Batch Analysis - explanation on 2-batch analysis, DACO: 2.13.1, 2.13.2, 2.13.3, CBI
2302289	2009, Appendix 1 - Confidential Statement of Formula, EPA Form 8570-4 and clarification, DACO: 2.1, 2.2, 2.3, 2.3.1, CBI
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2224617	2009, Physical and Chemical Properties of the Male Sea Lamprey Mating Pheromone End-Use Product, (3-ketopetromyzonol-24-sulfate, ammonium salt [CBI removed], DACO: 2.14.1, 2.14.13, 2.14.14, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9, 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.2, 3.5.3, 3.5.6, 3.5.7, 3.5.
2224621	2009, 3kPZS Technical Grade Active Ingredient and End-use Product Storage Stability and Corrosion Characteristics, DACO: 2.14.14, 3.5.10, 3.5.14.
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2.0 Human and Animal Health

PMRA Document Number	Reference
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2224574	2012, *In Vitro* Percutaneous Absorption of 3-ketopetromyzonol-24-sulfate, ammonium salt in Cadaver Skin Model, DACO: 4.2.2
2224575	2012, *In Vitro* Prediction of Acute Airway Irritation Using the MatTek EpiAirway Model, DACO: 4.2.3
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2224579	2012, *In Vitro* Prediction of Acute Dermal Irritation Using the MatTek EpiDerm Model, DACO: 4.2.5
2224581	2012, Skin Sensitization in 3-D Model: 1 Test Article, DACO: 4.2.6

2224583 2012, Waiver requests for tier 1 human health assessment subchronic testing, development toxicity, mutagenicity testing for 3kPZS TGAI, DACO: 4.3.1, 4.5.2, 4.5.3, 4.5.4, 4.5.5

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2301055 2010, Building a tiered approach to *in vitro* predictive toxicity screening: a focus on assays with the in vivo relevance, DACO: 4.2.1

2301056 Towards a new predictive method in toxicology? Case study with a multiparameter, cell-based *in vitro* model, DACO: 4.2.1

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2301058 2009, Estimation of acute oral toxicity using the No Observed Adverse Effect Level (NOAEL) from the 28 day repeated dose toxicity studies in rats, DACO: 4.2.1

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3.0 Environment

PMRA Document Number	Reference
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4.0 Value

PMRA Document Number	Reference
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